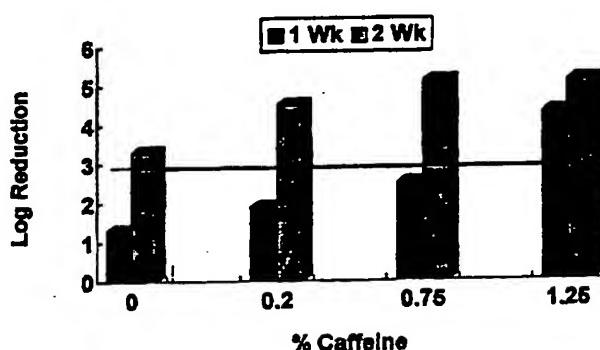


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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: TOPICAL OPHTHALMIC FORMULATIONS COMPRISING AN ACIDIC DRUG, VITAMIN E TPGS, BENZALKONIUM CHLORIDE AND CAFFEINE			

0.1% Diclofenac, 0.01% BAC, 1.5% TPGS► *S. aureus* PET screen

(57) Abstract

Stable, comfortable, preserved, topical, ophthalmic compositions of acid drugs and their use for treating inflammation of the eye are disclosed. The compositions contain an acidic drug (e.g. a NSAID, preferably diclofenac, or a prostaglandin), Vitamin E, TPGS, Benzalkonium chloride or homologues thereof and caffeine.

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TOPICAL OPHTHALMIC FORMULATIONS COMPRISING AN ACIDIC DRUG,
VITAMIN E TPGS, BENZALKONIUM CHLORIDE AND CAFFEINE

5 Field of the Invention

This application is directed to stable and comfortable preserved ophthalmic formulations containing an acidic drug.

10 Background of the Invention

Carboxyl containing compounds, including most non-steroidal antiinflammatory drugs (NSAIDs), are difficult to formulate into stable, preserved, comfortable, ophthalmic compositions. Acidic drugs with carboxyl groups are inherently irritating to the eye. In addition, the drugs tend to form insoluble complexes with quaternary ammonium preservatives, such as benzalkonium chloride (BAC). Many NSAIDs have been formulated with other than desirable preservatives (e.g. sorbic acid, thimerosol) because the compounds complex with desired preservatives, such as, quaternary ammonium compounds, particularly BAC. In addition, it has proved difficult to formulate carboxyl containing compounds that are comfortable when applied topically to the eye.

There are ophthalmic products containing acidic drugs. Commonly, these drugs are NSAIDs containing a carboxyl group. Examples of these products are suprofen (Profenal[®], Alcon Laboratories, Inc. which is preserved with thimerosol); diclofenac sodium (Voltaren OphthalmicTM, Ciba Vision Ophthalmics which is preserved with sorbic acid); flurbiprofen sodium (Ocufen[®], Allergan Medical Optics which is preserved with thimerosol); and ketorolac tromethamine (Acular[®], Allergan, Inc. which is preserved with BAC and Octoxynol 40).

30 U. S. Patent No. 5,110,493 discloses aqueous, ophthalmic, non-steroidal anti-inflammatory formulations which include a preservative system formed of a quaternary ammonium compound and a nonionic surfactant which is an ethoxylated alkyl phenol, such as Octoxynol 10 or 40.

WO 94/15597 discloses the use of lauralkonium chloride, a C₁₂ homologue of BAC, which is compatible with acidic drug entities in ophthalmic formulations.

U. S. Patent No. 4,960,799 discloses an ophthalmic formulation of a salt of ortho-(2,6-dichlorophenyl) aminophenylacetic acid, EDTA, a solubilizer, and a bacteriostat.

EP 0,621,036-A1 discloses ophthalmic formulations of particular arginine amides and either cyclodextrin or caffeine. The application discloses that the use of cyclodextrin or caffeine improves the arginine amide solubility in water and that the caffeine can stabilize the compound in water.

U. S. Patent No. 4,559,343 discloses ophthalmic formulations containing NSAIDs and a xanthine derivative to reduce ocular discomfort.

The compositions of the present invention are stable, yet they contain an acidic drug and the desired preservative, BAC, or mixtures of at least two homologues of BAC. In addition, the compositions are comfortable upon topical instillation in the eye.

Summary of the Invention

The present invention is directed to stable, comfortable, and preserved topical ophthalmic formulations comprising an acidic drug, Vitamin E Tocopherol Polyethylene Glycol 1000 Succinate (TPGS) (Eastman Chemical Co., Kingsport, TN), BAC, or mixtures of at least two homologues of BAC, and caffeine. Types of acidic drugs can include NSAIDs, antibacterials, diagnostic agents, antiinfective agents, and prostaglandins. Methods for the compositions' use are also disclosed.

Brief Description of the Drawing

Figure 1 shows the effect of caffeine concentration on the preservative efficacy of BAC.

Detailed Description of Preferred Embodiments

The compositions of the present invention comprise an acidic drug, Vitamin E TPGS, BAC, or mixtures of BAC homologues, such as C₁₂ and C₁₄ and caffeine. As used herein the term "acidic" means the drug contains a carboxyl moiety or a salt thereof and/or a sulfamide group or a salt thereof.

Acidic drugs which can be formulated according to the present invention include NSAIDs, including, but not limited to, diclofenac, bromfenac, flurbiprofen, naproxen, ketorolac, suprofen, ibuprofen, and tolmetin, including their pharmaceutically acceptable salts, esters, and prodrugs; prostaglandins; antibacterial and antiinfective agents; and diagnostic agents. BAC is used to preserve the formulations. The Vitamin E TPGS is used to solubilize the acidic drug and reduce ocular discomfort in aqueous conditions. The caffeine is added to reduce ocular discomfort, but surprisingly, it was found that it acts synergistically with Vitamin E TPGS to reduce discomfort and it also potentiates the preservative efficacy of BAC.

In the formulations, the acidic drug is present at concentrations from 0.001 weight percent (wt. %) to 2.5 wt. %, preferably 0.01 to 1.0 wt. %. The Vitamin E TPGS concentration is 0.0001 to 30 wt. %, preferably 0.01 to 10 wt. %. BAC or its homologue mixtures are present at concentrations from 0.00001 to 0.02 wt. %, preferably .0001 to 0.01 wt. %; and the caffeine concentration is from 0.001 to 5.0 wt. %, preferably 0.01 to 1.0 wt. %.

The compositions of the invention may also contain other components such as, but not limited to, those listed below:

1. Buffers (e.g., phosphate, borate, citrate, acetate, carbonate, borate-polyol complexes, etc.);
2. Tonicity agents (e.g. mannitol, sodium chloride, xylitol, etc.)
3. Viscosity building agents, e.g., carboxylic polymers like Carbopol® (carboxomers), Noveon® (polycarbophils), etc.; cellulose derivatives including alkyl and hydroxyalkyl cellulose like methylcellulose, hydroxypropylcellulose, carboxymethylcellulose, etc.; gums like locust beam, xanthan, agarose, karaya, guar, etc.; and other polymers including but not limited to polyvinyl alcohol, polyvinyl pyrrolidone, polyethylene glycol, Pluronic® (Poloxamers), tragacanth, and hyaluronic acid.
4. Phase-transition polymers for providing sustained and controlled delivery of enclosed medicaments to the eye (e.g., alginic acid, carrageenans (e.g., Eucheuma), xanthan and locust bean gum mixtures, pectins, cellulose acetate phthalate, alkylhydroxyalkyl cellulose and derivatives thereof, hydroxyalkylated polyacrylic acids and derivatives thereof, poloxamers and their derivatives, etc. The phase-transition in these polymers can be mediated by changes in environmental factors such as ionic strength, pH, or temperature alone or in combination with other factors.
5. Other excipients include but are not limited to: antioxidants (ascorbic acid, sodium metabisulfite, etc.), complexing agents (cyclodextrins and derivatives thereof), drug carriers or drug-laden ion exchange carriers, such as, Amberlite® and Duolite®, and some chelating agents.

The ophthalmic compositions can be administered topically to the eye as suspensions, emulsions, ointments, gels, or solutions. The compositions may be aqueous or nonaqueous, but are preferably aqueous. The compositions may have the drugs incorporated and/or encapsulated in microcapsules, nanocapsules, nanoparticles, or liposomes which are dispersed in an aqueous or nonaqueous medium.

The preferred formulation of this invention comprises diclofenac sodium, as illustrated in Example 2.

The following Examples are illustrative, but not limiting:

Examples 1 and 2 are useful in treating ophthalmic inflammation. The formulations are administered 1-4 times daily according to the routine discretion of a skilled clinician.

Example 1

<u>Ingredients</u>	<u>Concentration (%wt./vol.)</u>
NSAID	0.1 - 2.5
HPMC	0.05 - 1.0
Tromethamine	0.1 - 1.2
Boric Acid	0.01 - 1.0
Vit E TPGS	0.1 - 5.0
Caffeine	0.01 - 2.0
Manitol	2.0 - 4.4
Benzalkonium Chloride or its homologue mixtures	0.005 - 0.01
Disodium EDTA	0.01 - 0.1
HCl/NaOH	q.s. to pH 7.4
Purified Water	q.s. 100%

Compounding Procedure:

To a tared glass vessel containing purified water, first caffeine is added. The solution is stirred until the caffeine dissolves. Next, the rest of the ingredients are added

in the order given below and each ingredient is completely dissolved by stirring before the next one is added.

5
NSAID
Vitamin E TPGS
Tromethamine
Boric acid
Disodium EDTA
Benzalkonium chloride
Mannitol
HPMC
10

The formulation is then brought to 95% of its final weight. The pH is adjusted to about 7-7.4 using NaOH or HCl. The final weight is adjusted to 100% with purified water. The formulation's tonicity is 300 mOsm.

15
Example 2

<u>Ingredients</u>	<u>Concentration (% w/w)</u>
Diclofenac Sodium	0.1
HPMC	0.1
Tromethamine	1.2
Boric Acid	0.6
Vit E TPGS	2.0
Caffeine	0.2
Mannitol	4.2
Benzalkonium Chloride	0.01
Disodium EDTA	0.1
HCl/NaOH	q.s. pH 7.4
Purified Water	q.s. 100%

30
Compounding Procedure:

A. Preparing 10 % Vitamin E TPGS stock solution

35
Deionized water (70% of final weight of TPGS stock solution) was taken in a large beaker and brought to boiling with heat. The required quantity of Vitamin E TPGS

was added in small proportions under stirring. Final weight was adjusted to 100% with additional d.i. water after all of Vitamin E TPGS had gone in solution.

5 B. Preparing 2% HPMC (Hydroxypropyl methyl cellulose) stock solution

HPMC wad added in small proportions under constant stirring into a beaker containing deionized water which was 70% of final weight of HPMC stock solution. Final weight was adjusted to 100% with additional d.i. water after all of the added HPMC had dissolved completely.

10 C. Ingredients were added in the order suggested below and each ingredient was dissolved completely under constant stirring before the next one was added:

15 0.2 g of caffeine was weighed in a tared vessel containing a stir bar and d.i. water which is 40% of final weight. Then 0.1 g of diclofenac, 20 g of 10% Vitamin E TPGS stock solution, 1.2 g of tromethamine, 0.6 g of boric acid, 0.1 g of disodium EDTA, 0.01 g of BAC, 4.2 g of mannitol and 5 g of 2% HPMC stock solution were added sequentially. Weight was adjusted to 95% of final weight with d.i. water. Next, pH was measured and if necessary, it was adjusted to 7.4 with 0.1N NaOH or 0.1N HCl. Finally weight was adjusted to 100 g with additional d.i. water.

Example 3

Examples of other NSAID and prostaglandin formulations						
Formulation	% weight by volume					
Ingredient	A	B	C	D	E	F
Caffeine	0.2	0.2	0.2	0.2	0.2	0.2
Flurbiprofen Sodium	0.03	-	-	-	-	-
Bromfenac	-	0.05	-	-	-	-
Suprofen	-	-	0.25	-	-	-
Suprofen	-	-	-	0.25	-	-
Prostaglandin (PGE ₂)	-	-	-	-	0.1	-
Prostaglandin (PGF _{2α})	-	-	-	-	-	0.1
10% Vitamin E TPGS Stock Soln.	20.0	20.0	15.0	20.0	25.0	25.0
tromethamine	1.0	1.0	1.2	1.2	1.0	1.0
boric acid	0.6	0.6	0.6	0.6	0.6	0.6
Disodium EDTA	0.05	0.05	0.05	0.05	0.05	0.05
Benzalkonium Chloride (BAC)	0.01	0.01	-	0.01	0.01	-
C12 and C14 homologues of BAC (80:20)	-	-	0.01	-	-	0.01
Mannitol	4.2	4.2	3.8	3.8	4.0	4.0
2% HPMC Stock Soln.	15.0	15.0	15.0	15.0	15.0	15.0
0.1N NaOH or 0.1N HCl to adjust pH	7.4	7.4	7.4	7.4	7.4	7.4
Deionized water qs to	100	100	100	100	100	100

Compounding Procedure:

Formulations A-F are prepared by adding caffeine to a tared glass vessel containing deionized water. The solution is stirred until caffeine is dissolved. Next, the remaining ingredients are added sequentially as listed and after the previous ingredient has completely dissolved. The solution is then brought to 95% of final weight with water and the pH is adjusted to 7.4. The final weight is then made 100% with water.

Example 4

A simplified preservative efficacy screen based on the United States Pharmacopeia (USP) XXII, 1990 Antimicrobial Preservative Effectiveness standards was performed against *Staphylococcus aureus* for the compositions shown in the following table. The screen entailed challenging the formulations with the gram-positive bacteria, *S. aureus*, and sampling at 7 and 14 days. The initial preservative efficacy test for the formulations had indicated that the formulations had poor preservation only against *S. aureus*, whereas the formulations exhibited appropriate preservative efficacy according to USP against the other organisms such as gram-negative (*Pseudomonas aeruginosa*) and fungi (*Aspergillus niger*) at 7 and 14 days.

Formulation Ingredient	A	B	C	D
Caffeine	0.0	0.2	0.75	1.25
Diclofenac Sodium	0.1	0.1	0.1	0.1
Vitamin E TPGS	1.5	1.5	1.5	1.5
Tromethamine	1.2	1.2	1.2	1.2
Boric acid	0.6	0.6	0.6	0.6
Disodium EDTA	0.1	0.1	0.1	0.1
BAC	0.01	0.01	0.01	0.01
Mannitol	4.4	4.4	3.8	3.2
HPMC	0.1	0.1	0.1	0.1
NaOH or HCl, qs to adjust pH to	7.4	7.4	7.4	7.4
Purified Water, qs to	100	100	100	100

According to the USP preservative efficacy standards for *S. aureus*, a formulation has to exhibit a minimum of 3.0 log reduction on day 14 and no increase in count between 14 to 28 days. Figure 1 shows the results for the *S. aureus* screen for the formulations in the above table. The formulations had similar compositions except for the varying concentrations of caffeine from 0.0% to 1.25%. As shown in Figure 1, the higher the caffeine concentration in the formulation the higher was the *S. aureus* log reduction value. The figure also shows that the required 3.0 log reduction is achieved by 7 days at higher caffeine concentration rather than on 14 days.

The formulation of Example 2 above showed the *S. aureus* log reduction values of 3.1 and 5.1 on days 7 and 14, respectively, when the *S. aureus* screen was performed.

Thus, surprisingly caffeine was found to potentiate the preservative efficacy of BAC in the formulations of the invention.

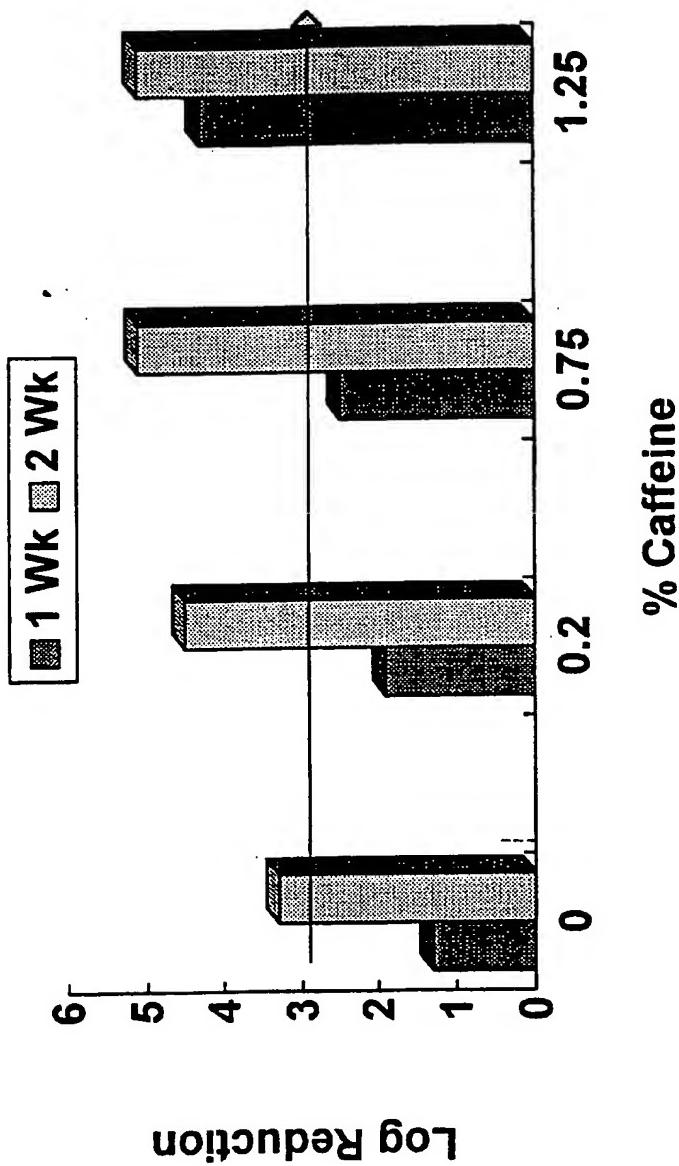
We Claim:

1. A topical ophthalmic composition comprising an acidic drug, Vitamin E TPGS, BAC or mixtures of at least two homologues of BAC, and caffeine.
- 5 2. The composition of Claim 1 having the following concentrations; 0.001 to 2.5 wt. % acidic drug; 0.0001 to 30 wt. % Vitamin E TPGS; 0.00001 to 0.02 wt. % BAC; and 0.001 to 5.0 wt. % caffeine.
- 10 3. The composition of Claim 2 wherein the acidic drug is selected from the group consisting of a NSAID and a prostaglandin.
4. The composition of Claim 3 wherein the acid drug is a NSAID.
- 15 5. The composition of Claim 4 wherein the NSAID is selected from the group consisting of diclofenac, bromfenac, flurbiprofen, naproxen, ketorolac, suprofen, ibuprofen, and tolmetin and their salts, esters, and prodrugs.
6. The composition of Claim 5 wherein the NSAID is diclofenac.
- 20 7. A topical ophthalmic composition comprising 0.01 to 2.5 wt. % NSAID, 0.0001 to 30 wt. % Vitamin E TPGS, 0.00001 to 0.02 wt. % BAC or mixtures of at least two homologues of BAC, and 0.001 to 5.0 wt. % caffeine.
- 25 8. The composition of Claim 7 wherein the NSAID is selected from the group consisting of diclofenac, bromfenac, flurbiprofen, naproxen, ketorolac, suprofen, ibuprofen, and tolmetin and their salts, esters, and prodrugs.
9. The composition of Claim 8 wherein the NSAID is diclofenac.
- 30 10. A method for treating inflammation of the eye, which comprises, applying the composition of Claim 7 to the inflamed eye.

11. The method of Claim 10 wherein the NSAID is diclofenac.
12. A method for treating an eye with an acidic drug, which comprises, applying the composition of Claim 1 to the eye.

Figure 1 0.1% Diclofenac, 0.01% BAC, 1.5% TPGS

> *S. aureus* PET screen



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/01976

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/557 A61K31/52 A61K9/00 A61K31/355 A61K31/40
 A61K31/38 A61K31/195 A61K31/19 //((A61K31/557,31:52,
 31:355),(A61K31/52,31:40,31:355),(A61K31/52,31:38,31:355)).

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO,A,95 30420 (ALCON LAB INC) 16 November 1995 see the whole document ---	1-12
Y	US,A,5 110 493 (CHERNG-CHYI ROGER F ET AL) 5 May 1992 cited in the application see the whole document ---	1-12
Y	WO,A,94 15597 (ALLERGAN INC) 21 July 1994 cited in the application see the whole document ---	1-12
Y	EP,A,0 163 924 (ROSHDY ISMAIL) 11 December 1985 see the whole document ---	1-12
	-/-	

Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

Date of mailing of the international search report

27 August 1996

06.09.96

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/01976

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (A61K31/52, 31:195, 31:355), (A61K31/52, 31:19, 31:355)

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,4 559 343 (HAN WESLEY W ET AL) 17 December 1985 cited in the application see the whole document see example 1 ---	1-12
Y	STP PHARMA SCIENCES, vol. 3, no. 3, 1993, pages 266-270, XP002011711 I. POPOVICI ET AL.: "Formulation et essais in vivo de collyres huileux d'indométacine" see the whole document ---	1-12 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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A document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 96/01976

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 9333 Derwent Publications Ltd., London, GB; AN 93-262882 XP002011713 & RO,A,105 131 (INST MEDICINA FARM IASI) , 25 July 1992 see abstract ---	1-12
Y	CONGR. INT. TECHNOL. PHARM./ 6TH, vol. 4, 1992, pages 254-262, XP002011712 M.W. ADAMS: "d-Alpha tocopheryl polyethylene glycol 1000 succinate (Eastman Vitamin E TPGS) as an emulsifier and bioenhancer for drugs and lipophilic compounds" see the whole document ---	1-12
Y	WO,A,93 03720 (TREVITHICK JOHN R) 4 March 1993 see the whole document -----	1-12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/01976

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 10-12 because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 10-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-12 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Reason: Compounds are not sufficiently defined as "acidic drug", "homologue s of BAC", "NSAID", "a prostaglandin", "prodrugs" etc. The search had to be limited to the substances explicitly mentioned in the claims and in the examples and to the general inventive concept.
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without incurring an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically, claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, i.e., claim No.:

Remark on Protest

- The required additional fees were accompanied by the applicant's protest
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/01976

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